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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/080,713	COLMAN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62,63,65,66,70-73,75-79,82,87-90,99,100,102-110,113,118-125,131 and 133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/14/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 62,63,65,66,70-73,75-79,82,87-90,99,100,102-110,113,118-125,131 and 133.

DETAILED ACTION

Applicants' Amendment and Response, filed 10/14/09, has been entered. Claims 62, 65, 66, 82, 90, 99, 100, 113, 121, 122, 131, 133 are amended; claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 are pending and under current examination.

Information Disclosure Statement

Applicants' IDS, filed 10/14/09, have been considered.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 62-69, 71-75, 78-86, 88-92,

95-97 of copending Application No. 11/641,644. Applicants provide no substantive arguments and state that they will address the rejection upon indication of allowable subject matter in the '713 case. Therefore, the rejection is maintained.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to overlapping subject matter. The instant claims are directed to producing non-human transgenic mammals, by modifying the nuclear genome of a fibroblast or other somatic cell that has a sufficient lifespan to be useful in genetic modification, and utilizing the cell in methods of nuclear transfer. The '644 claims are drawn to methods of producing genetically modified ungulates by modifying the nuclear genome of a somatic cell with a normal karyotype at an endogenous locus, utilizing the somatic cell in nuclear transfer methods to produce a genetically modified ungulate. The instant claims recite utilizing fibroblasts as the nuclear donor, the '644 claims recite utilizing fibroblasts (claim 77, for example). Additionally, the instant claims are directed to any transgenic mammal, and further embodiments are directed to ungulates including sheep, pig, cattle, and goat (claim 63, for example). The instant claims and the '644 claims both claim inactivation of a gene (claim 66 in the instant application, claim 67 of the '644 Application). Additionally, both sets of claims recite modifying the nuclear genome of the donor cell to inactivate α-1,3 galactosyltransferase (claims 123-124 of the instant application; claims 68, 85, 97 of the '644 claims); And modifying an endogenous immunoglobulin gene (claim 125 of the instant application; claims 71, 86 of the '644 claims). Accordingly, the '644 claims are rendered obvious in view of the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

New Matter

The prior rejection of claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for new matter, is withdrawn in view of Applicants' amendment to the claims, which no longer recite "fibroblast-like" cells.

Enablement

The prior rejection of claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 under 35 U.S.C. 112, first paragraph, is *withdrawn* in view of Applicants' amendment to the claims which longer recite utilizing a fibroblast-like cell as the donor nucleus.

Claim Rejections - 35 USC § 112

The prior rejection of claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 133 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Apps' amendment to the claims which no longer recite the term "fibroblast-like".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 62, 63, 65, 66, 75, 76, 82, 87-90, 99, 100, 106, 113, 118, 119, 120-122, 131 and 133 stand rejected under 35 U.S.C. 102(b) as anticipated by Campbell *et al.* (WO 97/07669, published 6 March 1997, Applicants' IDS).

Applicants' Arguments. Applicants argue that the claims have been amended to recite that the donor nuclear genome has been modified at a targeted site using homologous recombination. Applicants argue that Campbell does not teach any method of modifying the nuclear genome of a fibroblast cell at an endogenous locus via homologous recombination. See p. 9 of the Response.

Applicants present Kucherlapati (1996) as evidence that many different types of techniques were used to provide genetic modification in cell lines prior to the present invention, and that Applicants were the first to show that the specifically recited technique that includes homologous recombination at an endogenous locus in an animal with a normal karyotype would produce a viable, genetically targeted animal. Applicants argue that this is neither discussed nor exemplified in Campbell. See p. 9.

Applicants argue that Campbell does not teach the presently claimed method, and that there is no expectation of success in combining nuclear transfer techniques described in Campbell with genetic targeting somatic cells otherwise known in the art. Applicants argue that somatic cell targeting is not the invention, but the invention involves the combination of somatic cell targeting with nuclear transfer techniques to produce viable animals. Applicants argue that the invention cannot

be parsed into its parts, but addressed as a whole. Applicants argue that homologous recombination in somatic cells occurs at much lower frequency in somatic cells than in ES cells and that primary somatic cells have a lower frequency of homologous recombination than immortalized cells. Applicants argue that fibroblasts undergo crises of senescence when cultured for extended periods, and that somatic cells that have been cultured for extended periods were believed to be too compromised to produce viable animals. Applicants state that they have never agued that somatic cell targeting could not be achieved, but that the art recognized that it was an inefficient process that could not be combined with nuclear transfer to produce viable animals with any expectation of success. Applicants argue that the examiner has failed to provide any support as to why a person of ordinary skill in the art would have had any expectation that a viable animal with a targeted genetic modification could be successfully produced via homologous recombination of fibroblast cells and subsequent nuclear transfer cloning, as presently claimed. See page 10 of the Response. Applicants cite Arbones, Finn, Thyagarajan, and Porter as support for their arguments.

Response to Arguments. These arguments have been fully considered, but are not found to be persuasive.

In particular, Campbell teaches the modification of an endogenous gene by gene knockout, or gene knock in (p. 6, lines 29-34; p. 20, lines 10-12). One of ordinary skill in the art would recognize that a gene knockout or a gene knock in refers to a specific gene targeting event in a specific gene of interest. The Examiner provides Capecchi (**Scientific American**, 270(3): 34-41, 1994) as evidence to show that one skilled in the art, at the time of filing, would understand that a knockout or a knock in of a gene is accomplished by homologous recombination. Capecchi teaches how targeted gene replacement is accomplished in cultured cells (p. 36, Figure 1). Accordingly, one of skill in the art would readily appreciate that in reading Campbell, who state, for example, "An animal in whose germ line an

endogenous gene has been deleted, duplicated, activated or modified." (page 6 lines 29-34) would clearly understand that the cultured cells taught by Campbell could be specifically modified for germ line transmission to knock in or knockout a particular gene of interest in order to produce a transgenic animal. One of ordinary skill in the art would clearly understand that this would result from utilizing techniques of homologous recombination. Applicants have not distinguished the instantly claimed invention from that which is taught by Campbell. Campbell teaches using homologous recombination to achieve a specific genetic modification. Campbell teaches using these genetically modified cells in methods of nuclear transfer.

If Applicant feels the art is not enabling, and the claims cannot be distinguished from the art, then Applicant's claims must also lack enablement. It is up to Applicant to amend the claims to be enabled and distinguish from the art. However, the effect is inherent in the art applied, as the case law states if an invention and the art have the same structure all properties of one will be found in the other. Applicant is encouraged to amend the claims to overcome the art. See also, MPEP ¶2121.01 which states in part that, "A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985)."

The cited art of Arbonnes, Finn, Thyagarajan, Porter have been discussed previously. In particular, these pieces of art provide guidance to show that other somatic cell types can be specifically targeted. There is nothing in these pieces of art that teaches away or shows that specific targeting of a specific locus cannot occur. The Examiner responds to Applicants' arguments that although somatic targeting may be "inefficient", there is nothing to suggest that it would not work and could not work with regards to the methods taught by Campbell. Campbell

teach each and every step of the claimed invention, and therefore anticipate the claims. Applicants have not distinguished their invention from that which is taught by Campbell. Because the cited art of Campbell and Applicants are indistinguishable, Campbell properly anticipates the claimed invention.

In particular, regarding Applicants' arguments on page 11 of the Response, the Examiner maintains that there is no guidance to show that it was a well-established belief that viable animals with targeted genetic modifications could not be produced. Applicants have not provided any evidence to show that Campbell's methods would not work. Campbell provides sufficient guidance for the particular cell types, the particular type of genetic modification, and the methodologies to fulfill the limitations of the claims. Applicants' invention does not provide any method steps that distinguish from Campbell's teachings; thus, given Applicants' claimed invention is indistinguishable from Campbell's, the result of the methods must be the inherent and identical.

Regarding Applicants' citation of "Preparation of Feeder layers from primary Embryonic fibroblasts" with regard to the limitation of fibroblasts to 15-20 passages, it is noted that Clark states that sheep fetal fibroblasts can divide 80-100 times before replicative senescence or crisis. In fact, Clark states that a total of ~45 doublings to generate targeted cells for NT, and support using these cells stating, "Therefore, it is encouraging that populations of bovine fibroblasts retained their totipotentcy for nuclear transfer after more than 45 cell doublings and, indeed, that populations of donor somatic cells can be used." See page 268, col. 1-2. Thus, Clark clearly teaches that for nuclear transfer, fibroblasts from both sheep *and* bovine could be used for genetic targeting, because both are able to survive well over 45 doublings. Therefore, contrary to Applicants' arguments, Clark provides further evidence to show that fibroblasts could be used for homologous recombination methodologies to generated targeted cells for NT.

Accordingly, the prior rejection of record is proper and maintained.

Rejection

Campbell teach methods of producing transgenic animals via nuclear transfer (see Abstract). They teach methods of nuclear transfer, to introduce quiescent cells arrested at G0 into enucleated oocytes (p. 9, lines 1-3 and lines 29-31) and the fusion and activation of the resultant NT unit (page 13), the activation of the resultant cell (p. 14), and then the transferring of the embryo to a surrogate mother in order to develop the embryo to term (p. 15, lines 11-19; p. 18, lines 21-33; p. 20, lines 1-23). They teach that transgenic animals that can be produced by their methods pertain to animals wherein an endogenous gene has been, "deleted, duplicated, activated or modified ..." (p. 6, lines 29-34). They additionally suggest that these modified cell populations include gene additions, gene knockouts, gene knock ins and other gene modifications, and optionally the cells may be transfected with suitable constructs and with or without selectable markers (p. 20, lines 10-12). They teach that their methods can be used in to produce any animal (p. 5, lines 10+). They teach that the animal can be bred (p. 17, lines 15-19). They teach that the donor nucleus may contain one or more transgenes, and that this genetic modification may be introduced by methods such as electroporation, or lipofectin (p. 7, lines 1-11). They teach that the donor cell can be any somatic cell of normal karyotype, including fibroblasts (p. 7, lines 13+). They teach that the cells are quiescent and in G0 state (p. 8, lines 13-22). They teach serum starvation to produce the G0 cells (p. 8, lines 25-29).

Accordingly, given the teachings of Campbell, it would have been obvious for one of skill in the art to produce a transgenic animal, as that instantly claimed, with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to produce transgenic animals by nuclear transfer, as suggested by Campbell, to reduce the number of recipients, to increase numbers of founders using clonal donor cells, to allow subtle genetic alteration by gene

targeting, for the production of transgenic, not chimeric animals, and finally, for the selection of specific cells which have genetic modification(s) of interest, prior to the generation of the whole animal. See page 6, lines 1-20.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 63, 65, 66, 75, 82, 87-90, 99, 100, 106, 113, 118-122, 131 and 133 stand rejected under 35 U.S.C. 102(e) as being anticipated by US Pat. No. 6,147,276 (Issued November 14, 2006, filed February 19, 1997).

Applicants provide no substantive arguments regarding this rejection, therefore this rejection is maintained.

Regarding claims 62, 90, 131 and 133, the '276 patent teaches methods of nuclear transfer to produce transgenic mammals (Abstract). The '276 patent teaches that donor cells can be fibroblasts (col. 4, lines 10-11). The '276 patent teaches producing cloned animals by transferring the donor cell nucleus into an enucleated metaphase II oocyte (col. 5, lines 58+), the activation of the resultant NT unit (col. 6, lines 63+) and developing a cloned animal from the embryo (col. 7, lines 35-44). The '276 patent teaches that transgenic animals can be produced by the claimed methods (col. 3, lines 16-20).

Regarding claim 63, the '276 patent teaches producing sheep, goat, camels, pigs (col. 3, lines 6-9).

Regarding claims 65, 66, 99, 100, the '276 patent teaches that endogenous genes can be deleted, duplicated, activated or modified (col. 3, lines 43-54 and col. 10, lines 43-49).

Regarding claims 75, 76, 106 the '276 patent teaches that transgenesis may be employed with selectable markers (col. 10, lines 47-49).

Regarding claims 82, 113, the '276 patent teaches that the genetic modification can be produced by lipofection (col. 4, lines 63-64).

Regarding claims 87, 118, the '276 patent teaches utilizing fibroblasts as donor cells (col. 4, lines 10-11).

Regarding claims 88, 89, 119, 120, the '276 document teaches inducing quiescence and arrest the cells in G0 phase of the cell cycle by serum starvation (col. 9, lines 39-41; col. 10, lines 17-18).

Regarding claims 121, 122, the '276 document teaches transfection by electroporation (col. 3, lines 60-64).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 62, 63, 65, 66, 75-79, 82, 87-90, 99, 100, 106-110, 113, 118-124, 131 and 133 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of d'Apice *et al.* (U.S. Pat. No. 5,849,991 published December 15, 1998).

Applicants' Arguments. Applicants argue that the claims now recite homologous recombination, and argue similarly as above, that Campbell does not disclose or suggest the presently claimed methods. Applicants argue that although it was known that somatic cells and particularly fibroblasts cells could be genetically modified using homologous recombination, it was also well known that these cells were subject to senescence and related changes that made it unfeasible to combine NT techniques with somatic cell homologous recombination. Applicants argue that d'Apice provides no additional information to overcome this deficiency.

Applicants argue that d'Apice relates to ES cells, and ES cells are not somatic cells. Applicants argue the techniques described in d'Apice differ dramatically from somatic cell NT, and that although transgenic animals have been produced using ES cells prior to the present invention, ES cells do not exhibit the low frequency of integration, senescence and other cell culture related changes that are exhibited by somatic cells. See pages 13-14 of the Response.

Response to Arguments. These arguments have been fully considered, but are not persuasive. Campbell fulfill the limitations of the claims. There is nothing that distinguishes the claimed invention from that which is taught by Campbell. Particularly, Campbell teach that transgenic animals can be made, by using a cell such as a fibroblast. This is exactly what is claimed. Applicants have not distinguished their invention from that which is taught and suggested by Campbell. Although one of skill in the art would recognize the general problems of the art, with regard to gene targeting somatic cells, Campbell provides specific guidance as to the cell types to use, as well as the techniques to produce the desired result. Although Applicants argue that Campbell does not provide any techniques to overcome the art-recognized difficulties in gene targeting somatic cells, and provide art to support these arguments, it is noted that the claims do not provide any steps that are distinguished from the teachings of Campbell. Therefore, the suggestion that Campbell is unpredictable, or non-enabling, suggests that Applicants' invention might similarly be unpredictable or non-enabling. The method steps, as instantly claimed, are not distinguished from the teachings of Campbell, and therefore, the prior rejection of record is maintained. If Applicant feels the art is not enabling, and the claims cannot be distinguished from the art, then Applicant's claims must also lack enablement. It is up to Applicant to amend the claims to be enabled and distinguish from the art.

d'Apice is not relied upon with regard to producing animals by NT. Campbell provides the required teachings for producing transgenic ungulates via NT, and

d'Apice discusses producing mammals, including but not limited to, mice, lacking alpha 1-3 galactosyltransferase (col. 4, lines 54-60). Therefore, the combination of the references sufficiently motivate the skilled artisan to arrive at the claimed invention, given Campbell's teachings for increasing efficiency of producing transgenic animals, and further, given d'Apice's teachings for the need in the art to produce animals whose organs can then be used for xenotransplantation, wherein the knockout of the alpha 1-3 galactosyltransferase gene reduces or eliminates the hyperacute rejection response. The rejection is maintained.

Claims 62, 63, 65, 66, 70, 73, 75-77, 82, 87-90, 99, 100, 102, 105-108, 113, 118-122, 125, 131, 133 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of Kucherlapati *et al.* (**WO 94/02602**, published February 3, 1994).

Applicants provide the same arguments regarding this rejection as that regarding d'Apice. The Examiner has addressed these arguments above.

Claims 62, 63, 65, 66, 70, 72, 75, 76, 82, 87-90, 99, 100, 102, 104, 106, 113, 118-122, 131 and 133 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of US Pat. No. 6,013,857 (Filed June 5, 1995, Issued January 11, 2000).

Applicants' Arguments. Applicants argue that Campbell does not anticipate or render obvious the methods recited in the independent claims and nothing in the '857 patent overcomes these deficiencies. Applicants argue that the '857 patent provides no direction to making targeted genetic modification in fibroblast cells by homologous recombination and combine this with SCNT.

Response to Arguments. These arguments have been fully considered but not persuasive. Applicants' arguments regarding Campbell have been addressed above. The '972 reference is not provided with regard to SCNT, but is provided with regard

to utilizing their methods in order to increase expression of an endogenous gene by non-homologous or illegitimate recombination, and the resultant transgenic cell can be used to express a particular gene product *in vivo* (col. 22, lines 8-10, for example) and the resultant transgenic animal can then produce the gene product to be isolated (col. 42, lines 56-60). Accordingly, the combination of Campbell and the '972 reference provide sufficient teachings, guidance and motivation to arrive at the claimed invention.

Claims 62, 63, 65, 66, 70, 71, 75, 76, 82, 87-90, 99, 100, 102, 103, 106, 113, 118, 119, 120-122, 131 and 133 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of Bedalov (**Journal of Biol. Chem.**, 269(7): 4903-4909, 1994) when taken with Rossert (**The J. of Cell Biol.** 129(5): 1421-1432, 1995).

Applicants provide the same arguments regarding Campbell. The Examiner has addressed these arguments above.

Campbell is described above. They do not specifically teach placing a transgene adjacent to an endogenous promoter in the nuclear genome wherein the promoter is a collagen gene promoter. However, prior to the time of the claimed invention, Bedalov discuss a transgene containing the COL1A1 promoter fused to a reporter gene and discuss its expression in a variety of mesenchymal cell types, including fibroblasts, osteoblasts and odontoblasts (see p. 4903, 1st col., 1st ¶). Bedalov teaches that transgenic mice which have ~3.5 kb of COL1A1 upstream promoter have strong expression of the reporter gene in high collagen producing tissues, such as tendon, bone and skin (p. 4903, col. 2, first full ¶). Bedalov teach that the COL1A1 construct, including the COL1A1 promoter confers tissue-specific expression in transgenic animals, with no aberrant expression (see pp. 4908-4909, bridging sentence). Bedalov suggest that making transgenic animals with genome-integrated transgenes would allow for further analysis of endogenous gene

expression and would provide a model that is more biologically representative for the interaction of trans-acting factors with the sequences in the promoter (p. 4909, 1st full ¶, last sentence).

Accordingly, it would have been obvious for one of ordinary skill in the art, to utilize the teachings to make a transgenic, gene targeted animal, by nuclear transfer, as taught by Campbell, and specifically target a transgene under the expression of a collagen promoter, such as that taught by Bedalov, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification in view of Bedalov's teachings, which show an art-recognized need to further analyze the expression of the COL1A1 promoter in transgenic animals, and additionally, in view of Rossert, who teach that the precise sequences responsible for the lineage-specific expression of the collagen promoter have not been defined (p. 1421, col. 2, last bridging ¶). Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632